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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/091,300	03/04/2002	Patricia Rockwell	11245/46211	1694

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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 12/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/091,300	ROCKWELL ET AL.	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,16-26,28,62,63,65 and 67* is/are pending in the application.

4a) Of the above claim(s) *15,27,29-61,64 and 66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,16-26,28,62,63,65 and 67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-9, 16-21, 28, 62, 63, 65 and 67 in part and claims 10-14 and 22-26 in Paper No. 7 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 15, 27, 29-61, 64, and 66 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

3. Claims 1-14, 16-26, 28, 62, 63, 65 and 67 are under examination. Claims 1-14, 16-26, 28, 62, 63, 65 and 67 will be examined to the extent such that the antagonists are antibodies that bind VEGFR and EGFR as set forth in the restriction requirement filed as Paper No. 6.

Specification

4. The disclosure is objected to because of the following informalities:

a. The priority statement on the first line of the specification should be updated to indicate the patent numbers of U.S. Application Nos. 09/401,163 (U.S. Patent No. 6,365,157) and 08/967,113 (U.S. Patent No. 6,448,077).

b. The specification should be updated to indicate the patent numbers of all U.S applications issued to date. For example, see page 20 U.S. Application No. 07/813,593 is now U.S. Patent No. 5,185,438. Applicant is reminded to check the entire disclosure for pendency of all U.S. Application Nos.

Appropriate correction is required.

Claim Objections

5. Claim 1 and 62 are objected to because of the following informalities:

a. Claim 1 and 62 are broadly drawn to a non-elected invention. Claims 1 and 62 are drawn to VEGFR and EGFR antagonists, which encompasses small molecules comprising oligosaccharides, polysaccharides, polypeptides, proteins, amino acids, oligo and polynucleotides, nucleosides, derivatives of biological molecules including lipid and glycosylation derivatives, organic compounds, organometallic compounds, small molecule derivatives and small inorganic compounds. The claims are being examined to the extent that the VEGFR and EGFR antagonists are antibodies.

Appropriate correction is required.

Priority

6. The instant claims are directed to anti-VEGFR and anti-EGFR antibodies in a method of inhibiting tumor growth in humans. Support for the instantly claimed method

can be found in the parent application (09/798,689), however, the grandparent application (09/401,163) does not have support for tumor inhibition methods consisting of antibodies that bind to VEGFR and EGFR. The instant claims are granted the priority date of 3/2/2001 (09/798,689).

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-14, 16-26, 28, 62-63, 65 and 67 are rejected under 35 U.S.C. 103(a) as being obvious over Rockwell et al (U.S. Patent 6,448,077 B1, filed 11/10/1997) in view of Petit et al (American Journal of Pathology. 151(6):1523-1530, 1997) as evidenced by Kawamoto et al (American Journal of Pathology. 151(6):1523-1530).

Claims 1-14, 16-26, 28, 62-63, 65 and 67 are drawn to a method of inhibiting tumor growth comprising administering to a human a vascular endothelial growth factor receptor (VEGFR) antagonist and an epidermal growth factor receptor (EGFR) antagonist wherein the antagonists are chimeric, humanized or human antibodies and the administration further comprises a chemotherapeutic agent or radiation and kits comprising such.

Rockwell et al teach chimeric and humanized anti-VEGFR antibodies that inhibit the interaction between vascular ependothelial growth factor (VEGF) and its receptor by binding to a VEGFR and thereby preventing VEGF phosphorylation of the receptor. Rockwell et al teach anti-VEGFR antibodies, monoclonal antibody DC101 and monoclonal antibody 6.12, which binds human flt-1 (see column 8). Rockwell et al also teach that DC101 reacted with two human VEGFR forms expressed in A431 tumor cells and DC101 inhibited tumor growth and demonstrated therapeutic value as an anti-angiogenic reagent against vascularized tumors secreting VEGF (see columns 21-23, examples VI and VII. Rockwell et al teach that VEGF and its receptors (VEGFR) are

upregulated in tumor cells and since VEGF expression is low in normal cells not associated with angiogenesis they would not be affected by blocking the VEGF-VEGFR interaction to inhibit angiogenesis, and therefore tumor growth (see column 2). Rockwell et al teach that the antibodies can be administered orally or intravenously (see column 6, lines 18-22) and the anti-VEGFR antibodies can be used for treating colorectal (i.e., colon) tumors and non-small cell lung tumors (see column 6, lines 43-52). Rockwell et al teach "the combined treatment of one or more of the antibodies of the invention with an anti-neoplastic or chemotherapeutic drug such as, for example, doxorubicin, cisplatin or taxol provides an even more efficient treatment for inhibiting the growth of tumor cells than the use of the antibody itself (see column 7, lines 17-27). Rockwell et al do not specifically teach anti-EGFR antibodies.

Petit et al teach a method of inhibiting tumor growth with a chimeric version of the anti-EGFR 225 antibody (C225) as evidenced by Kawamoto et al (see page 1525). Petit et al teach that EGFR as an inducer of VEGF and, hence, by extension tumor angiogenesis. Petit et al teach that VEGF is a ubiquitous tumor angiogenesis factor. Petit et al teach that treatment of the A431 human epidermoid carcinoma with the anti-EGFR monoclonal antibody, C225, resulted in a dose-dependent inhibition of VEGF expression at both the mRNA and protein levels in vitro and in vivo (see pages 1526-1527 and 1529). Petit et al also teach that C225 is being evaluated in "early-phase clinical trials, either alone or in combination with various cytotoxic anti-cancer chemotherapeutic drugs with which they may synergize" (see page 1524, left column).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a method of inhibiting tumor growth in humans comprising administering antibodies that bind VEGFR and EGFR and a chemotherapeutic agent or radiation for therapeutic benefit of human tumors.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to produce a method of inhibiting tumor growth in humans comprising administering antibodies that bind VEGFR and EGFR and a chemotherapeutic agent or radiation for therapeutic benefit of human tumors in view of Rockwell et al and Petit et al as evidenced by Kawamoto et al because Rockwell et al teach anti-VEGFR antibody, DC101, inhibited tumor growth and demonstrated therapeutic value as an anti-angiogenic reagent against vascularized tumors secreting VEGF and Rockwell et al state that "the combined treatment of one or more of the antibodies of thee invention with an anti-neoplastic or chemotherapeutic drug such as, for example, doxorubicin, cisplatin or taxol provides an even more efficient treatment for inhibiting the growth of tumor cells than the use of the antibody itself". In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to produce a method of inhibiting tumor growth in humans comprising administering antibodies that bind VEGFR and EGFR and a chemotherapeutic agent or radiation for therapeutic benefit of human tumors in view of Rockwell et al and Petit et al as evidenced by Kawamoto et al because Petit et al teach EGFR as an inducer of VEGF and, hence, by extension tumor angiogenesis and treatment of the A431 human epidermoid carcinoma with the anti-EGFR antibody,

C225, which inhibits the growth of established A431 tumors resulted in a dose-dependent inhibition of VEGF expression at both the mRNA and protein levels in vitro and in vivo. Additionally, Petit et al acknowledge that anti-EGFR antibodies in combination with various cytotoxic anti-cancer chemotherapeutic drugs may synergize tumor inhibition. Therefore, it is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06. Thus, it would have been obvious to one skilled in the art to produce a method of inhibiting tumor growth in humans comprising administering antibodies that bind VEGFR and EGFR and a chemotherapeutic agent or radiation for therapeutic benefit of human tumors in view of Rockwell et al and Petit et al as evidenced by Kawamoto et al.

Although the claims recite a kit, no positive recitation of the kit ingredients/elements distinguishes the claim over the references. Therefore, the references read on the claimed kit. Further, it is a well-known convention in the art to place the recited elements in a kit for the advantages of convenience and economy.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

9. Claims 1-5, 7-14, 16-17, 19-26, 28, 62-63, 65 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rockwell et al (Molecular and Cellular

Differentiation. 3(4): 315-335, 1995, Ids # 6) in view of Queen et al (U.S. Patent No. 5,530,101, filed 12/19/1990) and Fan et al (Cancer Research 53: 4637-4642, 1993) and Siemeister et al (Cancer and Metastasis Reviews 17: 241-248, 1998).

Claims 1-5, 7-14, 16-17, 19-26, 28, 62-63, 65 and 67 have been described supra.

Rockwell et al teach a method of using neutralizing monoclonal antibodies to target protein tyrosine kinase receptors (i.e., EGFR and VEGFR) that play a role in malignant transformation. Rockwell et al teach that overexpression of EGFR correlates with poor prognosis for many cancers, including breast, prostate, non-small cell lung carcinoma, bladder, head and neck, and ovarian carcinomas (see page 317). Rockwell et al teach monoclonal antibodies 225 and 528 that bind EGFR and inhibit ligand binding and a chimeric version of monoclonal antibody 225 (C225) binds EGFR with five- to ten-fold higher affinity than 225 (see page 317). The 225 antibody is able to inhibit the growth of A431 (human epidermoid carcinoma) xenogratfs in nude mice when given within 5 days of tumor inoculation, but was unable to inhibit the growth of well-established A431 tumors (see page 317). Rockwell et al teach that monoclonal antibodies 225 and 528 effectively induced regression of established A431 or MDA-468 (breast carcinoma) xenografts when combined with chemotherapeutic agents such as doxorubicin or cisplatin. Further, C225 plus cisplatin induced a statistically significant inhibition of the growth of KB (human epidermoid carcinoma cell line) xenografts in nude mice despite the fact that either antibody or cisplatin alone were ineffective and a similar observation was seen in the A431 (human epidermoid carcinoma cell line) model (see page 317 and Figure 1). Rockwell et al also teach a VEGFR-specific monoclonal

antibody, DC101, which blocked VEGF receptor activation in the A431 tumor cell line (see page 322 and Figure 4A and 4B) and DC101 significantly inhibited the growth of new and established tumors (see page 323). Rockwell et al teach that DC101 is cross-reactive with human VEGFR receptor forms (i.e., flt-1 and KDR) and thus, has the potential to inhibit VEGF-mediated activation of receptors on endothelial cells induced to proliferate and form blood vessels during tumor angiogenesis (see page 323). Rockwell et al teach that VEGFR expression is unregulated in endothelial cells associated with chronic hypoxia in lung tissue and during tumor formation for glioblastomas, hemangioblastomas and ovarian carcinomas (see page 322). Rockwell et al also teach a monoclonal antibody (71E1) to flk-2 that cross-reacts with both mouse and human forms of the receptor with the ability to neutralize flk-2 activation (see page 327). Finally, Rockwell et al attest to the "mounting preclinical and clinical data that combination therapies may be more efficacious than single agent use" (see page 327).

Rockwell et al do not specifically teach antibody humanization or chimeric VEGFR antibodies or upregulation of VEGFR receptors in tumors or expression of EGFR in colon carcinomas or intravenous administration. These deficiencies are made up for in the teachings of Queen et al and Fan et al and Siemeister et al.

Queen et al teach chimeric antibodies wherein mouse variable regions are joined to human constant regions (see column 11, lines 53-65), human and humanized antibodies comprising CDRs from non-human donor VH and VL chains and human framework regions and a human constant region and the humanized antibody binds the same antigen as the non-human donor antibody, providing the CDRs (see columns 2-3,

12-16). Queen et al teach that most monoclonal antibodies do not fix human complement well, are immunogenic when injected in human patients (i.e. human anti-mouse antibody response; HAMA) and subsequent treatments with non-human antibodies, even for unrelated therapies, can be ineffective or even dangerous because of cross-reactivity (see column 1, lines 33-54). Queen et al teach the advantages of humanized antibodies over mouse antibodies in human therapy. Because the effector portion (i.e., constant region) is human, humanized antibodies are expected to i) interact better with the human immune system (i.e., CDC and ADCC), ii) reduce the HAMA response and iii) the humanized antibodies will "presumably have a longer half-life more similar to naturally occurring human antibodies, allowing smaller and less frequent doses to be given" (see column 16, lines 6-26). Queen et al teach that the antibodies can be administered intravenously (see column 23, lines 22-25) the antibodies can be supplied as kits (see column 24, lines 41-43).

Fan et al teach anti-EGFR monoclonal antibodies 225 and 528 that inhibit proliferation of a variety of cultured malignant human cell lines, including colon (see page 4637). Fan et al also teach that combination therapy of tumors with monoclonal antibody 225 plus the chemotherapeutic agent cis-diamminedichloroplatinum (cis-DDP) substantially inhibited tumor growth when compared to individual treatments with either monoclonal antibody 225 or cis-DDP alone (see Figure 2).

Siemeister et al teach that VEGFR receptors (flt-1 and KDR/flk-1) are up-regulated "when angiogenesis takes place, as in the case of tumor growth" (see page 243, right column). Siemeister et al teach that "the growth of malignant tumors is

associated with tissue hypoxia and hypoxia has been described to be a major mechanism leading to the up-regulation of VEGF and its receptors in vivo" (see page 244). Siemeister et al teach that decreased VEGF expression in tumor cells has been achieved by blocking EGF-stimulated expression of VEGF in A431 tumor cells using an anti-EGFR neutralizing antibody (see page 245).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method for inhibiting tumor growth comprising antibodies that bind VEGFR and EGFR and a chemotherapeutic agent and used the method of Queen et al to produce VEGFR and EGFR chimeric and humanized antibodies to increase effector function (i.e., CDC and ADCC), reduce HAMA responses and increase antibody half-life for therapeutic benefit of human tumors.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method for inhibiting tumor growth comprising antibodies that bind VEGFR and EGFR and a chemotherapeutic agent and used the method of Queen et al to produce VEGFR and EGFR chimeric and humanized antibodies to increase effector function (i.e., CDC and ADCC), reduce HAMA responses and increase antibody half-life for therapeutic benefit of human tumors in view of Rockwell et al and Queen et al and Fan et al and Siemeister et al because Rockwell et al teach EGFR- and VEGFR-specific antibodies (225 and DC101, respectively) that were effective at inhibiting A431 tumor cell growth and Rockwell et al and Fan et al also teach combination therapy wherein a synergistic inhibitory affect of

A431 tumors was observed with monoclonal antibody 225 and a chemotherapeutic agent when compared with either 225 or chemotherapeutic agent alone. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method for inhibiting tumor growth comprising antibodies that bind VEGFR and EGFR and a chemotherapeutic agent and used the method of Queen et al to produce VEGFR and EGFR chimeric and humanized antibodies to increase effector function (i.e., CDC and ADCC), reduce HAMA responses and increase antibody half-life for therapeutic benefit of human tumors in view of Rockwell et al and Queen et al and Fan et al and Siemeister et al because Queen et al teach chimeric and humanized antibodies, which increase effector function (i.e., CDC and ADCC), reduce HAMA responses and increase antibody half-life for human therapy and Rockwell et al teach a chimeric version (C225) of monoclonal antibody 225 that binds to the EGFR with five- to tenfold higher affinity than 225. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to produce a method for inhibiting tumor growth comprising antibodies that bind VEGFR and EGFR and a chemotherapeutic agent and used the method of Queen et al to produce VEGFR and EGFR chimeric and humanized antibodies to increase effector function (i.e., CDC and ADCC), reduce HAMA responses and increase antibody half-life for therapeutic benefit of human tumors in view of Rockwell et al and Queen et al and Fan et al and Siemeister et al because Rockwell et al teach that VEGFR expression is unregulated in endothelial cells associated with chronic hypoxia in lung tissue (i.e., lung carcinomas) and Siemeister et al teach that "the growth of malignant

tumors is associated with tissue hypoxia and hypoxia has been described to be a major mechanism leading to the up-regulation of VEGF and its receptors in vivo" and an anti-EGFR receptor neutralizing antibody decreased VEGF expression in A431 tumor cells. Therefore, it would have been obvious to produce a highly efficacious method for inhibiting tumor growth in humans by combining anti-VEGFR and anti-EGFR antibodies as well as a chemotherapeutic agent because anti-EGFR and anti-VEGFR were individually shown to inhibit human A431 tumors and the antibodies behaved synergistically when combined with a chemotherapeutic agent and anti-EGFR antibodies were also shown to decrease VEGF production, providing additional synergism for tumor inhibition. It is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

Thus, it would have been obvious to one skilled in the art to produce a method for inhibiting tumor growth comprising antibodies that bind VEGFR and EGFR and a chemotherapeutic agent and used the method of Queen et al to produce VEGFR and EGFR chimeric and humanized antibodies to increase effector function (i.e., CDC and ADCC), reduce HAMA responses and increase antibody half-life for therapeutic benefit of human tumors in view of Rockwell et al and Queen et al and Fan et al and Siemeister et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1, 5, 7-8, 10-14, 17, 19-26, 28, 62-63, 65 and 67 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 15, 17, 25-26 and 32 of copending Application No. 09/798,689 in view of Queen et al. Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant claims are drawn to a method of inhibiting tumor growth comprising administering to a human a vascular endothelial growth factor receptor (VEGFR) antagonist and an epidermal growth factor receptor (EGFR) antagonist wherein the

antagonists are chimeric, humanized or human antibodies and the administration further comprises a chemotherapeutic agent or radiation and kits comprising such.

The conflicting claims in Application No. 09/798,689 are drawn to a method for reducing tumor growth in a mammal with a combination of a VEGFR antagonist and radiation or a chemotherapeutic agent wherein the mammal is a human and the VEGFR antagonist is a monoclonal antibody and the method further comprises an EGFR antagonist. The claims in 09/434,870 do not teach chimeric, human or humanized antibodies or intravenous administration or kits comprising antibodies. These deficiencies are made up for in the teachings of Queen et al.

Queen et al teach chimeric antibodies wherein mouse variable regions are joined to human constant regions (see column 11, lines 53-65), human and humanized antibodies comprising CDRs from non-human donor VH and VL chains and human framework regions and a human constant region and the humanized antibody binds the same antigen as the non-human donor antibody, providing the CDRs (see columns 2-3, 12-16). Queen et al teach that most monoclonal antibodies do not fix human complement well, are immunogenic when injected in human patients (i.e. human anti-mouse antibody response; HAMA) and subsequent treatments with non-human antibodies, even for unrelated therapies, can be ineffective or even dangerous because of cross-reactivity (see column 1, lines 33-54). Queen et al teach the advantages of humanized antibodies over mouse antibodies in human therapy. Because the effector portion (i.e., constant region) is human, humanized antibodies are expected to i) interact better with the human immune system (i.e., CDC and ADCC), ii) reduce the HAMA

response and iii) the humanized antibodies will "presumably have a longer half-life more similar to naturally occurring human antibodies, allowing smaller and less frequent doses to be given" (see column 16, lines 6-26). Queen et al teach chemotherapeutic agents and the humanized immunoglobulins may be utilized alone or together with a chemotherapeutic agent (see column 19, lines 37-67 and column 20, lines 1-15). Queen et al teach that the antibodies can be administered intravenously (see column 23, lines 22-25) and the antibodies can be supplied as kits (see column 24, lines 41-43).

The claims in the instant application are obvious variants of Application No. 09/798,689 because it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced chimeric and humanized anti-VEGFR and anti-EGFR antibodies to increase effector function (i.e., CDC and ADCC), reduce HAMA responses and increase antibody half-life for therapeutic benefit of human tumors.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced chimeric and humanized anti-VEGFR and anti-EGFR antibodies to increase effector function (i.e., CDC and ADCC), reduce HAMA responses and increase antibody half-life for therapeutic benefit of human tumors in view of Queen et al because Queen et al teach Because the effector portion (i.e., constant region) is human, humanized antibodies are expected to i) interact better with the human immune system (i.e., CDC and ADCC), ii) reduce the HAMA response and iii) the humanized antibodies will "presumably have a longer half-life more similar to naturally occurring human antibodies, allowing smaller and less frequent

doses to be given" and Queen et al teach chemotherapeutic agents, intravenous administration and kits comprising antibodies.

This is a provisional obviousness-type double patenting rejection.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number through January 19, 2004 is (703) 605-1200. The examiner can be reached at (571) 272-0827 after January 21, 2004. The examiner can normally be reached at (703) 605-1200 from 8:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, can be reached at (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1123.

Official papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The official fax number for Group 1600 where this application or proceeding is assigned is (703) 872-9306.

Respectfully,
David J. Blanchard
703-605-1200

LARRY R. HELMS, PH.D
PRIMARY EXAMINER

LARRY R. HELMS, PH.D
PRIMARY EXAMINER